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The impact of ketamine on emergency rapid sequence intubation: a systematic review and meta-analysis

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Abstract

Background Rapid sequence intubation (RSI) is a crucial step in the resuscitation process for critically ill patients, and the judicious use of sedative drugs during RSI significantly influences the clinical outcomes of patients. Ketamine is a commonly used anesthetic sedative; however, its impact on the mortality of patients undergoing RSI has yielded inconsistent findings. Therefore, we conducted a systematic review and meta-analysis investigating ketamine's role in RSI to provide insights into selecting appropriate sedatives for critically ill patients.

Methods In this systematic review and meta-analysis, we conducted a systematic search on MEDLINE (PubMed), Embase, and Cochrane Central Register of Controlled Trials, without restricting to randomized controlled trials (RCTs) or cohort studies. The search was performed from inception until Dec 12, 2023, with no language restrictions. All studies comparing the use of sedatives, including ketamine, and documenting in-hospital mortality were included in this study.

Results A total of 991 studies were identified, out of which 15 studies (5 RCTs and 10 cohort studies) involving 16,807 participants fulfilled the inclusion criteria. No significant impact on in-hospital mortality was observed with the use of ketamine compared to other drugs during RSI (OR 0.90, 95%CI 0.72 to 1.12). Low-quality evidence suggested that ketamine might reduce mortality within the first seven days of hospitalization (OR 0.42, 95%CI 0.19 to 0.93), but it may also have a potential effect on prolonging ICU-free days at day 28 (MD -0.71, 95%CI -1.38 to -0.05). There were no significant differences in the results of the other RSI-related outcomes, such as physiological function and adverse events.

Conclusions Based on existing studies, ketamine showed no significant difference compared to other sedatives in terms of in-hospital mortality, physiological impact, and side effects following RSI. However, it may reduce mortality within 7 days while probably prolong the length of stay in the ICU.

Trial registration CRD42023478020.

Keywords Ketamine, Rapid sequence intubation, Resuscitation, Mortality

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Introduction

Rapidly establishing a secure airway significantly enhances treatment success during the resuscitation of critically ill patients. Emergency endotracheal intubation is a pivotal step. Typically, this process involves rapid sequence intubation (RSI), which requires the rapid and sequential administration of sedatives and neuromuscular blocking agents [1]. Currently, various medications such as ketamine, propofol, and etomidate, are commonly used for sedation before intubation in RSI, with global variations in usage patterns [2, 3]. Due to the fragile physiology of critically ill patients, the selection of the most appropriate sedative drug during intubation is a big challenge for clinicians. In addition to considering its impact on patient mortality, factors such as sedation depth and post-intubation physiological changes must be considered. Inadequate sedation depth may lead to patient restlessness, impacting the intubation procedure, while excessive sedation can result in a sudden decline in blood pressure, heart rate, and myocardial function, causing multi-organ perfusion insufficiency and impeding patient recovery. Therefore, an optimal RSI agent should have rapid onset of action, negligible hemodynamic effects, limited impact on organ function, and minimal related side effects. Importantly, the use of sedatives should not contribute to increased patient mortality.

In pursuing the optimal sedative for RSI, researchers have examined the impact of different drugs on in-hospital mortality through prospective and retrospective studies, yielding inconsistent results [3–5]. Ketamine, commonly used in critically ill patients with trauma or infections, offers specificities such as rapid onset and increased pulse rate in healthy individuals through catecholamine release, making it potentially suitable for hemodynamically unstable critically ill patients [6]. However, it may induce hallucinations and nightmares [7]. Compared to etomidate, ketamine may pose a higher risk of hypotension during RSI, especially in patients with catecholamine depletion [8, 9]. In addition to ketamine and etomidate, other sedative agents are also employed by emergency physicians or prehospital emergency care providers during RSI [2, 10].

Given the distinct pharmacological profiles of different sedatives used in RSI, we conduct this systematic review and meta-analysis to compare the impact of various medications used for intubation in critically ill patients undergoing emergency airway management on patient outcomes.

Methods

Search strategy

This systematic review and meta-analysis was conducted and reported by the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [11]. This review has been registered in PROSPERO (registration number: CRD42023478020). To prevent the inadvertent omission of pertinent research during the retrieval process, we conducted an initial literature search. The following keywords were used to search in the PubMed, Embase, and Cochrane Library databases: ((Ketamine [Mesh]) OR (2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone) OR (CI-581) OR (CI 581) OR CI581 OR Ketalar OR Ketaset OR Ketanest OR Calipsol OR Kalipsol OR Calypsol OR (Ketamine Hydrochloride)) AND ((Rapid Sequence Induction and Intubation [Mesh]) OR (Rapid Sequence Intubation) OR (Intubation, Rapid Sequence) OR (Rapid Sequence Induction) OR (Emergency Endotracheal Intubation) OR (Emergency Intubation)). The search period ranged from inception to 12 December 2023. For a comprehensive evaluation of the role of ketamine in Rapid Sequence Intubation (RSI), the included literature encompasses not only randomized controlled trials (RCTs) but also cohort studies. However, to address heterogeneity, distinct analysis will be undertaken when evaluating mortality rates. Subsequently, each study underwent meticulous scrutiny following the PICOS (population, intervention, comparison, outcome, and study design) criteria. The decision to incorporate a particular study into our meta-analysis was then made based on the outcomes of this thorough evaluation. There were no restrictions on the publication date. Additionally, to ensure comprehensive coverage, a review of the reference lists of relevant studies was conducted. All identified papers underwent inclusion in the EndNote X9 software for initial screening. Following this, duplicate citations were eliminated, and unpublished as well as conference studies were excluded from further consideration. The inclusion criteria for this meta-analysis were defined as follows: 1. Inclusion of studies where ketamine was utilized as a sedative agent in the context of RSI, with a comparative analysis against other pharmacological agents. 2. Recorded outcomes encompassed hospital mortality rates, including overall in-hospital mortality, mortality within 7 days, and mortality within 28 days. 3. The study provides specific details about the location of RSI implementation, such as air ambulance, pre-hospital, trauma center, emergency department, emergency ICUs, etc., excluding operating rooms. Clinical trials incorporating additional intervention groups were treated as distinct and individual studies. In instances where multiple published articles existed for a singular dataset, priority was accorded to the dataset with the most comprehensive data for inclusion in the analysis. The exclusion criteria for this study encompass experimental research, review articles, case reports, and investigations centered on pathological mechanisms. Furthermore, studies lacking

reported mortality rates or those specifically addressing RSI conducted within an operating room setting will be excluded.

Data extraction

Two independent researchers extracted data from each qualified RCT and cohort study. The extracted information includes name of the first author, publication year, study design, country, individuals' characteristics (mean age, and sex), sample size (control and intervention groups), the location of endotracheal intubation, the reasons for requiring endotracheal intubation (if multiple diseases necessitate intubation, recorded the primary disease), medications administered before intubation (including sedatives, analgesics, and neuromuscular blocking agents used in the study), physiological status before and after intubation (including recorded systolic blood pressure, heart rate, SOFA score, APACHE II score, ISS score), first-attempt intubation success rate, the mortality rate (7 days, 28 days, and during hospitalization), length of stay in the intensive care unit (ICU) and hospital, duration of mechanical ventilation (MV), and complications during intubation (including cardiac arrest, intubation failure, hypotension, etc.). We tried to contact the authors for more information if data were missing.

Quality assessment

For different types of studies, we employ distinct methodologies for quality assessment. The Cochrane quality assessment tool [12] was used to assess the risk of bias for RCT studies, and Newcastle–Ottawa Scale (NOS) [13] was utilized to assess the risk of bias for nonrandomized studies. Two independent investigators (QX H and X L) assessed the risk of bias in each included study and a third investigator (CL W) was consulted to resolve any disagreements.

Statistical analysis

We used Revman (version 5.4; Cochrane Collaboration, Oxford, UK) and Stata (version 17.0; Stata Corp LP) for statistical analysis. Odds ratio (OR) with 95% confidence intervals (CIs) for dichotomous data was used as the effect measure. The interquartile ranges (IQRs) were converted to mean and SDs according to the method of Luo et al. [14] and Wan et al. [15]. To derive the comprehensive effect sizes, we employed a random-effects model, considering variations between studies. I^2 statistics and the Cochran Q test were used to detect the heterogeneity between the included studies, and a value of $I^2 > 50\%$ or $P < 0.05$ for the Q test was considered as significant heterogeneity between studies [16]. To identify probable sources of heterogeneity, meta-regression was conducted according to the variables including type of study (RCT vs. cohort study), country (western country vs. east country), the location of endotracheal intubation (in-hospital vs. pre-hospital), the reasons for requiring endotracheal intubation (trauma vs. respiratory vs. others), the size of the sample population (large-the enrolled patients > 100 vs. small-the enrolled patients < 100), mean age (< 60 vs. ≥ 60 years old), and intervention drugs (etomidate vs. propofol vs. others). Besides, subgroup analysis was conducted according to the variables including the mortality of different time point (7 days vs. 28 days vs. others) and adverse events during intubation (cardiac arrest vs. post-intubation hypotension vs. others). In the pursuit of uncovering potential sources of heterogeneity, we will additionally conduct subgroup analysis when the meta-regression reveals a significance level of $P < 0.05$. A sensitivity analysis was conducted to assess the impact of individual studies on the overall effect size. To determine the publication bias, Begg's test and Egger's test were used, as well as visual inspection of the funnel plot. In the presence of identified publication bias, we conducted an adjustment of the summary estimate utilizing trim-and-fill analysis [17]. $P < 0.05$ was considered statistically significant.

Results

Study selection

The systematic literature search identified 991 publications of which 15 articles ultimately met the inclusion criteria (5 RCTs [3, 18–21] and 10 cohort studies [2, 5, 10, 22–28] (Fig. 1). The results of search strategy were shown in Supplementary Text 1. During the literature assessment, detailed information on excluded studies is available in Supplementary Text 2.

Study characteristics

The detailed information of the included studies is present in Table 1. In total, the studies comprised 13,802 participants and 3005 patients treated with ketamine during RSI. Among the included studies, 11 utilized etomidate as the control group, while 1 employed propofol as the control group [3, 18–21, 23–28]. Additionally, 1 study used a combined control group consisting of different sedation drugs (etomidate, propofol, midazolam) excluding ketamine [22], another study employed etomidate, sodium thiopental, and midazolam as separate control groups [10], and 1 study compared etomidate and propofol as distinct control groups [5]. Among the 15 studies included, 2 were characterized by relatively small sample sizes (the enrolled patients < 100) [10, 23], while the remaining 13 were considered large-sample studies (the enrolled patients ≥ 100) [2, 3, 5, 18–22, 24–28]. 12 studies were

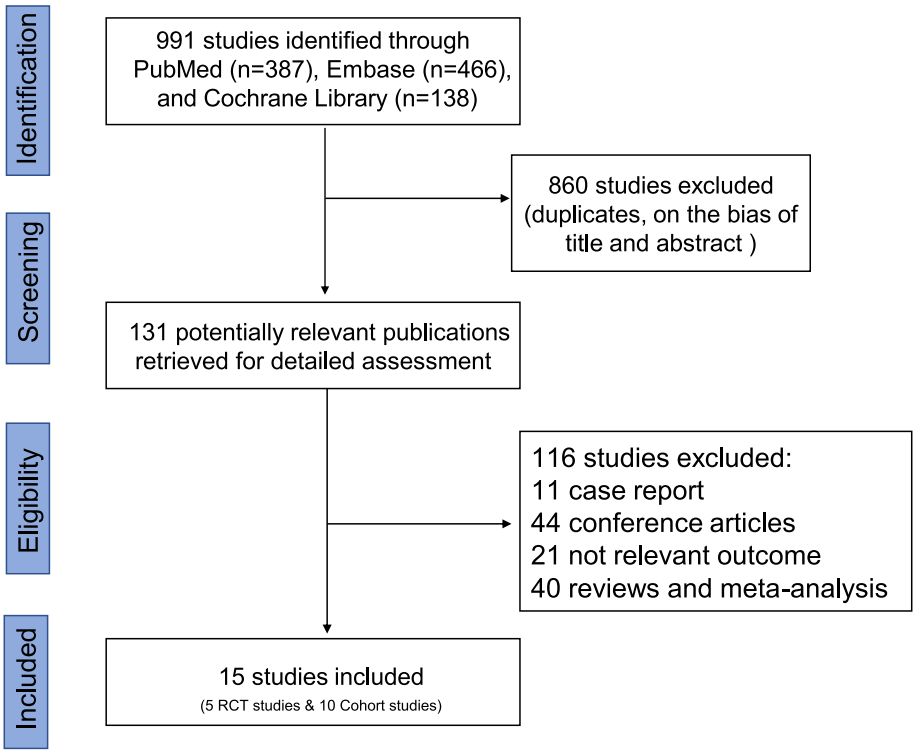

Fig. 1 PRISMA flow diagram of study selection

conducted in Western countries, comprising 4 RCT studies [3, 18–20] and 7 cohort studies [2, 5, 22–24, 26, 27]. The remaining 3 studies originated from Eastern countries, including 1 RCT study [21] and 2 cohort studies [10, 25]. Regarding the average age of the study populations, 3 studies enrolled participants with an average age below 60 years [10, 21, 28], whereas the remaining studies enrolled populations with an average age exceeding 60 years [2, 3, 5, 18–20, 22–27]. Additionally, 8 studies exclusively focused on RSI conducted within the emergency department [3, 5, 18–21, 24, 27], while the rest were performed in pre-hospital, medical ICU, or other locations [2, 10, 22, 23, 25, 26, 28].

Study quality and risk of *bias*

Given the inclusion of both RCTs and cohort studies in this meta-analysis, risk of bias assessment was performed using the Cochrane quality assessment tool and the Newcastle–Ottawa Scale, respectively. Detailed assessment results can be found in Supplementary Fig. 1 and Supplementary Table 1. The included 5 RCTs exhibited as 'low risk' to 'some concerns', with no study identified as 'high risk'. The cohort studies achieved NOS scores ranging from 6 to 9. The overall assessment of the quality of all the included research was moderate.

Effect of ketamine on hospital mortality after RSI

The results of the meta-analysis encompassing the relevant studies, conducted through a random-effects model, demonstrated no statistically significant difference between ketamine and alternative sedation medications concerning overall in-hospital mortality (OR = 0.90, 95% CI = 0.72–1.12) (Fig. 2A). There was relatively high heterogeneity among these studies (I^2 = 59%, P-heterogeneity = 0.0008). To further explore the sources of heterogeneity, we conducted meta-regression analysis using study type, country, location of endotracheal intubation, reasons for endotracheal intubation, sample population size, and intervention drugs as potential sources of heterogeneity. The results of the meta-regression analysis indicated that the sample size included in the studies may be a source of heterogeneity. Therefore, we conducted subgroup analysis for this variable, revealing that meta-analysis of studies with smaller sample sizes (< 100) suggested a potential reduction in in-hospital mortality after RSI with ketamine treatment, while the analysis of studies with larger sample sizes (≥ 100) did not show significant differences (Supplementary Fig. 2). It is noteworthy that studies with smaller sample sizes have lower credibility and may inherently possess higher bias. The results of the sensitivity analysis indicated that the exclusion of any individual study did not impact the overall estimate

Table 1 Characteristics of included studies

Author	Year	Study design	Country	Main diagnosis	Number of patients		Number (%) women	Mean age (years)	Drugs		Neuromuscularar relaxants	Intubation location
					Treatment	Control			Treatment	Control	Treatment	
April	2020	RCT	USA	Trauma	738	6068	2270 (33)	49	Ketamine	Etomidate	Rocuronium, Succinylcholine, Vecuronium	ED
Baekgaard	2020	Cohort	Denmark	Trauma	111	155	69 (26)	49	Ketamine	Mixed (Etomidate, propofol, or midazolam)	Rocuronium, Suxamethonium, Vecuronium	Pre-hospital & Trauma Center
Breindahl	2021	Cohort	Denmark	Trauma	228	320	137 (25)	50	Ketamine	Propofol	Rocuronium, Suxamethonium, or combined	Pre-hospital & Trauma Center
Cornelius	2018	Cohort	USA	Trauma	15	47	NA	46	Ketamine	Etomidate	NA	Pre-hospital
Edalatkhah (E)	2021	Cohort	Iran	COVID-19	8	12	6 (30)	62	Ketamine	Etomidate	NA	Inpatient
Edalatkhah (M)	2021	Cohort	Iran	COVID-19	8	35	14 (33)	67	Ketamine	Midazolam	NA	Inpatient
Edalatkhah (T)	2021	Cohort	Iran	COVID-19	8	21	11 (38)	60	Ketamine	Sodium thiopental	NA	Inpatient
Foster	2022	Cohort	USA	NA	86	272	110 (31)	56	Ketamine	Etomidate	Rocuronium, Succinylcholine	ED
Jabre	2009	RCT	USA	Trauma	235	234	NA	58	Ketamine	Etomidate	Succinylcholine	ED
Kim	2023	Cohort	Korea	Trauma	118	354	105 (17)	51	Ketamine	Etomidate	NA	Trauma bay
Knack	2023	RCT	USA	Medical	70	73	52 (36)	49	Ketamine	Etomidate	Rocuronium, Succinylcholine	ED
Leede (E)	2021	Cohort	USA	Trauma	169	1786	427 (22)	43	Ketamine	Etomidate	NA	ED
Leede (P)	2021	Cohort	USA	Trauma	169	137	51 (17)	40	Ketamine	Propofol	NA	ED
Lyon	2015	Cohort	UK	Trauma	145	116	44 (19)	42	Ketamine	Etomidate	Rocuronium	Pre-hospital
Matchett	2021	RCT	USA	Shock	395	396	303 (38)	56	Ketamine	Etomidate	Rocuronium, Succinylcholine	ED
Srivilaithon	2023	RCT	Thailand	Sepsis	130	130	107 (41)	72	Ketamine	Etomidate	Succinylcholine	ED
Upchurch	2017	Cohort	USA	Trauma	442	526	261 (27)	40	Ketamine	Etomidate	Succinylcholine	ED
Van	2017	Cohort	USA	Respiratory failure	115	115	109 (47)	60	Ketamine	Etomidate	NA	Medical ICU

ED Emergency department, *NA* Not available

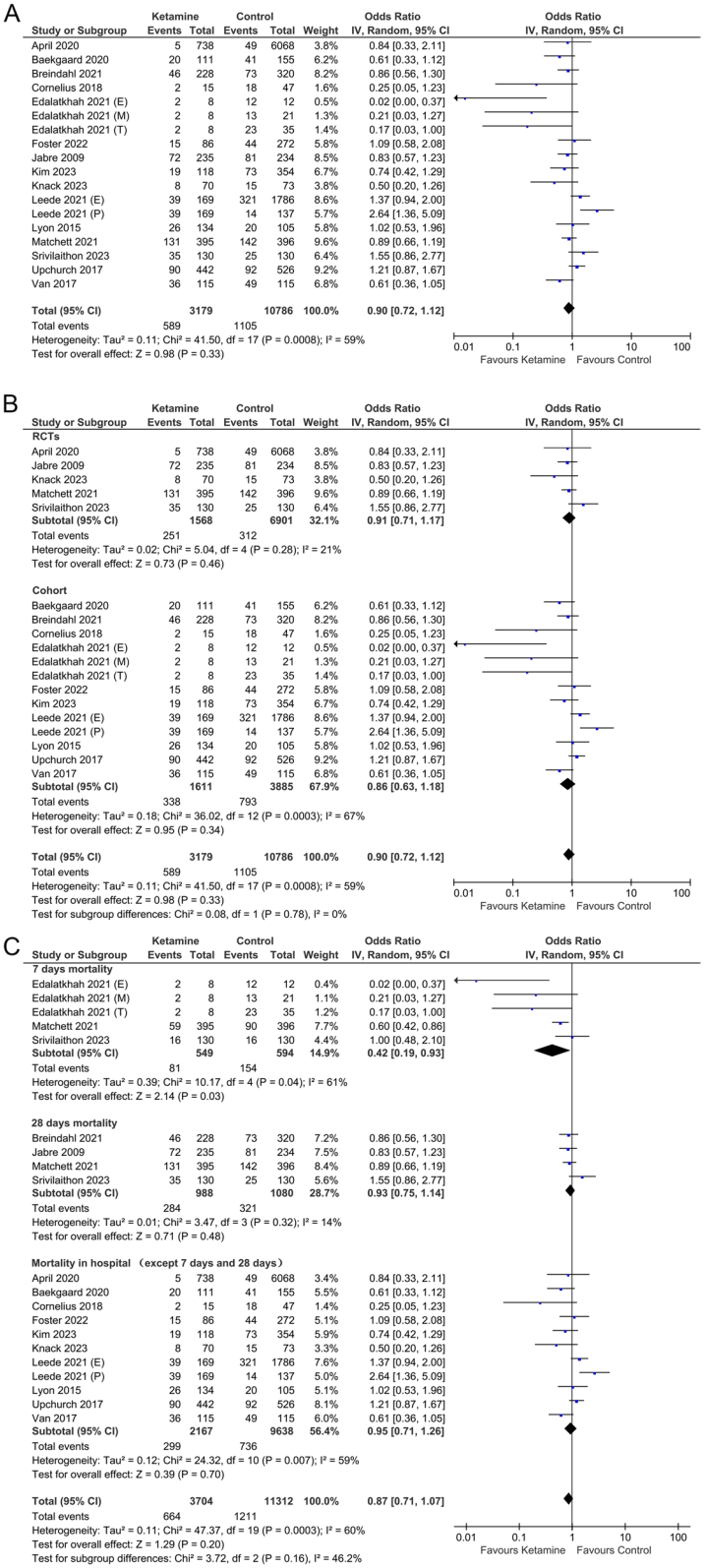

Fig. 2 The effect of ketamine on in-hospital mortality after RSI. **A** total in hospital mortality; **B** subgroup analysis of different study design; **C** subgroup analysis of mortality in different time points

of the effects of ketamine on in-hospital mortality (Supplementary Fig. 3).

We conducted separate examinations for RCTs and cohort studies. Interestingly, when focusing solely on RCTs, a slight reduction in heterogeneity was observed (I^2 = 21%, P-heterogeneity = 0.28). However, the meta-analysis results still did not indicate an association between the use of ketamine for RSI or an increased mortality rate during the hospitalization period (OR = 0.91, 95% CI = 0.71–1.17). Conversely, the analysis considering only cohort studies showed a slight increase in heterogeneity (I^2 = 67%, P-heterogeneity = 0.0003), yet the results remained statistically unchanged (OR = 0.90, 95% CI = 0.72–1.12) (Fig. 2B).

To conduct a more detailed comparison of mortality differences among patients undergoing RSI with ketamine and other medications at different time points, we analyzed mortality rates separately for 7 days, 28 days, and unspecified time frames post-admission. Subgroup analysis results revealed that among the 3 studies focusing on mortality within the first 7 days [10, 20, 21], comprising a total of 5 comparative groups, ketamine significantly reduced mortality rates within the initial 7 days (OR = 0.42, 95% CI = 0.19–0.93). Nevertheless, its impact on mortality rates within the first 28 days was not statistically significant [2, 3, 20, 21](OR = 0.93, 95% CI = 0.75–1.14) (Fig. 2C). Upon visually inspecting the funnel plot, asymmetry was evident (Fig. 3). Subsequent Begg's (P = 0.028) and Egger's (P = 0.024) regression tests confirmed the presence of significant publication bias. After the trim and fill method conducted, the summary result remained unchanged (OR = 1.00, 95% CI = 0.79–1.28) (Supplementary Fig. 4).

Effect of ketamine on RSI related outcomes

To comprehensively assess the impact of ketamine and other medications on the outcomes of RSI, we conducted separate analysis of intubation-related changes, including changes in systolic blood pressure (SBP) and heart rate (HR) before and after intubation, as well as the success rate of the first intubation attempt. Additionally, we evaluated post-intubation outcomes during hospitalization, encompassing the length of stay in the ICU and the hospital, ICU-free days at day 28, MV duration, MV-free days at day 28, changes in Sequential Organ Failure Assessment (SOFA) scores.

Initially, we assessed the changes in vital signs following RSI, with SBP and HR serving as representative indicators. The results indicated that the use of ketamine during RSI did not result in significant alterations in SBP (MD = 5.72, 95% CI = -5.40–16.84) (Fig. 4A) and HR (MD = 0.14, 95% CI = -1.49–1.77) (Fig. 4B). Meanwhile, we assessed the first-attempt intubation success rate following the administration of various sedative agents. The results demonstrated that ketamine showed no significant difference compared to other medications (OR = 1.08, 95% CI = 0.77–1.51) (Supplementary Fig. 5A).

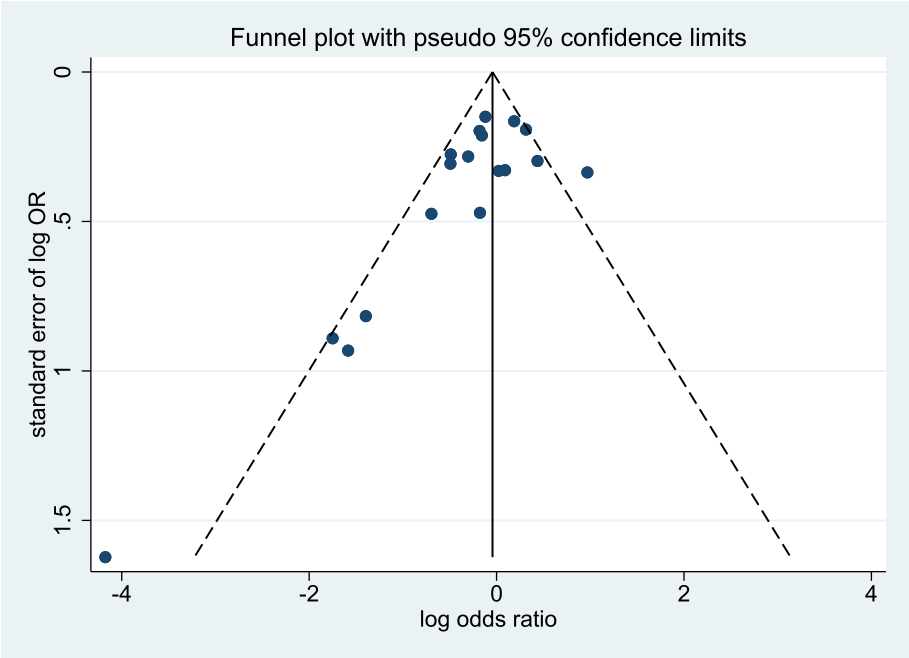

Fig. 3 Funnel plot of the effect of ketamine on in-hospital mortality after RSI

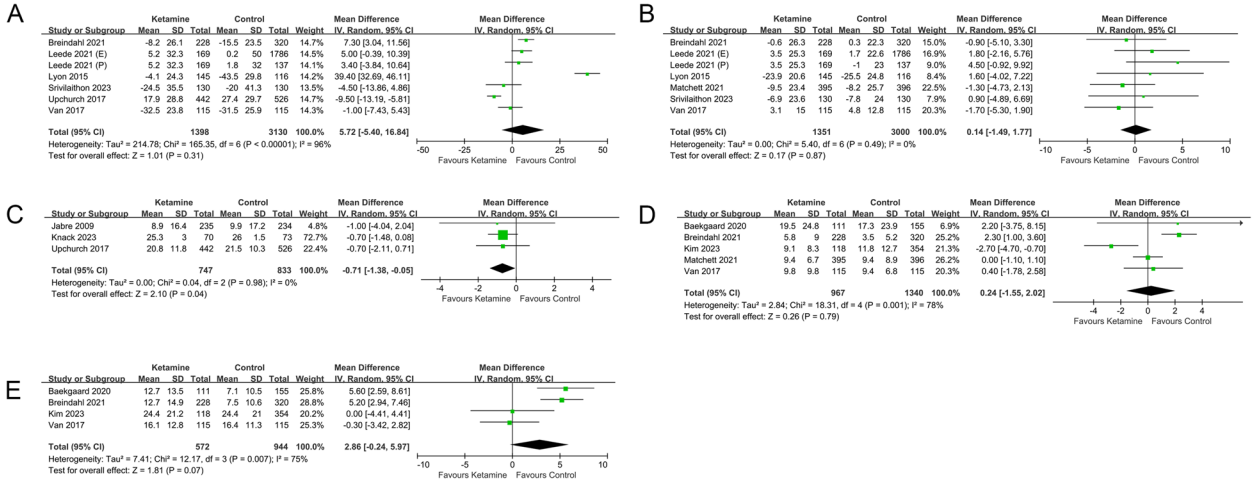

Fig. 4 The effect of ketamine on RSI-related outcomes. **A** change of systolic blood pressure; **B** change of heart rate; **C** ICU-free days at day 28; **D** length of stay in ICU; **E** length of stay in hospital

Besides, we also examined the patient outcomes during hospitalization following RSI. The analysis suggested that ketamine may reduce the ICU-free days at day 28 compared to other medications (MD = -0.71, 95% CI = -1.38–1.77) (Fig. 4C). However, no significant differences were observed in MV duration (MD_{MV} = -0.80, 95% CI = -2.20–0.61, Supplementary Fig. 5B), MV-free days at day 28 ($MD_{MV\text{-}28}$ = -0.36, 95% CI = -0.96–0.25, Supplementary Fig. 5C), length of stay in the ICU and hospital (MD_{ICU} = 0.24, 95% CI = -1.55–2.02, $MD_{hospital}$ = 2.86, 95% CI = -0.24–5.97, Fig. 4D-E), or the change in SOFA score after intubation (MD_{SOFA} = -0.01, 95% CI = -0.32–0.31) (Supplementary Fig. 5D).

Effect of ketamine on intubation related adverse events

In the course of clinical practice, besides observing the efficacy of relevant drugs or techniques, attention must also be paid to the complications associated with the treatment protocol. Therefore, we analyzed the incidence of possible complications related to the use of medications or RSI practice during the RSI process, including occurrences such as cardiac arrest and post-intubation hypotension. In general, the use of various anesthetic or sedative drugs during RSI did not significantly alter the incidence of totally complications (OR = 1.20, 95% CI = 0.83–1.73) (Fig. 5A). Similarly, when separately evaluating the incidence of specific complications, no significant differences were observed between ketamine and other drugs in events such as cardiac arrest and post-intubation hypotension ($OR_{cardiac\ arrest}$ = 1.18, 95% CI = 0.72–1.94; $OR_{post\text{-}intubation\ hypotension}$ = 1.32, 95% CI = 0.89–1.95) (Fig. 5B-C).

Discussion

The results of our primary meta-analysis, encompassing 3005 critically ill patients across 15 studies, revealed no significant difference in overall in-hospital mortality during RSI between ketamine and other sedation medications. After conducting separate analysis on various types of included studies and performing a meta-regression analysis that considered several factors influencing in-hospital mortality, the results showed no significant differences. Although ketamine did not exhibit a significant effect on the 28-day mortality after RSI, there may be a potential reduction in mortality within the initial 7 days. Except for a potential prolongation of ICU stay after RSI, the administration of ketamine and other interventions exhibited no discernible effects on hemodynamics, mechanical ventilation duration, SOFA scores, or other pathophysiological parameters. In comparison to other medications, ketamine demonstrated no significant impact on adverse effects associated with RSI.

In order to promptly manage the airway or ensure adequate oxygenation in critically ill patients, RSI is commonly performed following the administration of sedatives and neuromuscular blocking agents in conditions such as trauma, severe pneumonia, and other critical emergencies. In a retrospective analysis by Hoffmann et al. [29] revealed that intubated patients with a Glasgow Coma Scale (GCS) of 8 or less had a lower mortality than non-intubated patients. Additionally, mortality was lower in patients who received sedation before intubation compared to those who did not.

Due to the limited number of relevant studies on the effect of different drugs on mortality after RSI, unlike the inclusion criteria for the meta-analysis by Baekgaard [30] et al., we did not restrict the literature based

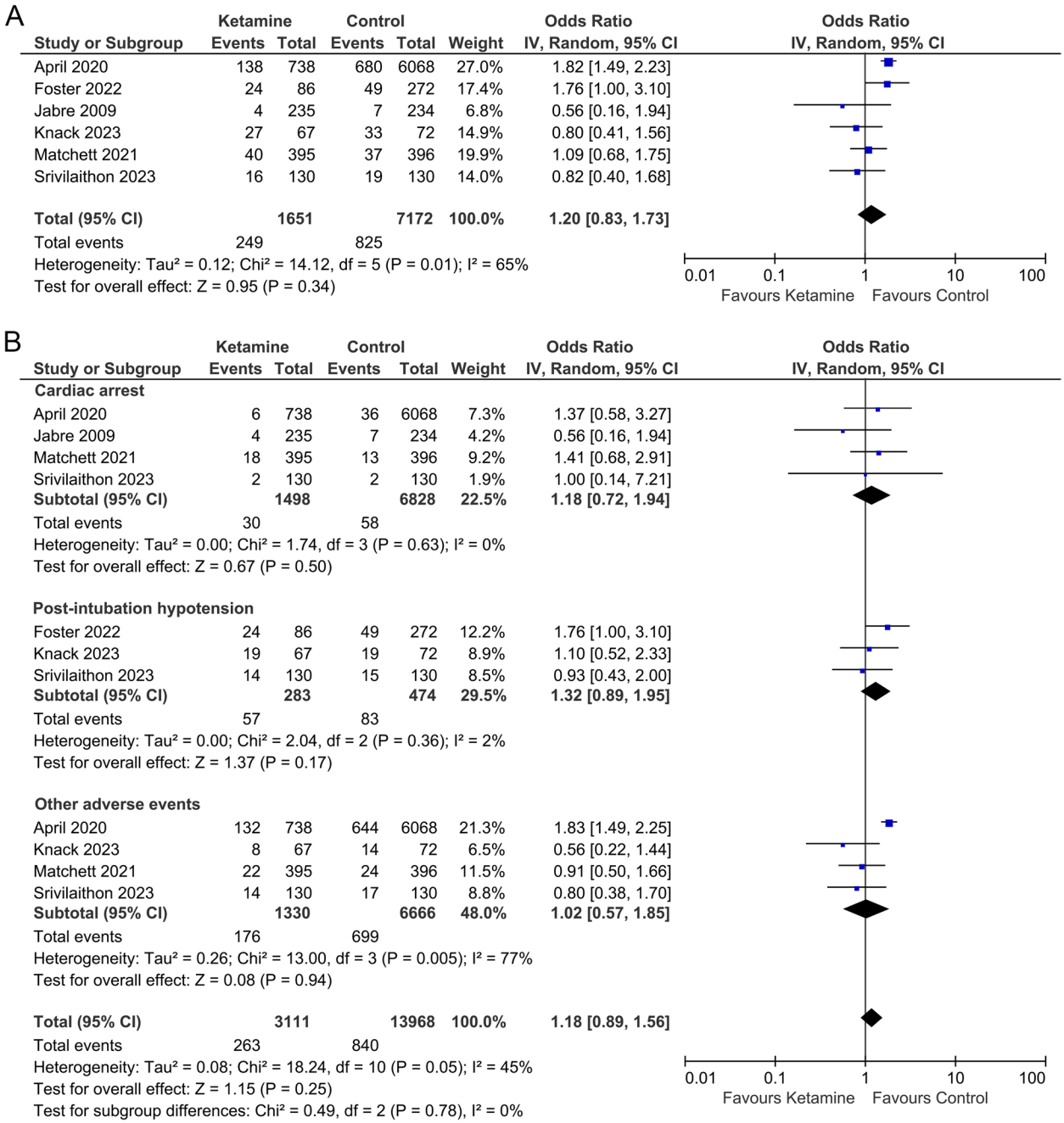

Fig. 5 The effect of ketamine on RSI-related adverse events. **A** total adverse events; **B** subgroup analysis of different adverse events, including cardiac arrest, post-intubation hypotension, and others

on study type or the disease condition of the included population to facilitate a more comprehensive evaluation. After expanding the inclusion criteria, we used a random-effects model in this meta-analysis and a relatively high heterogeneity was found. However, the meta-regression analysis and necessary subgroup analysis on six potential sources of study heterogeneity revealed no significant impact on overall in-hospital mortality rates. After we conducted a quality assessment of included literature, identified potential sources of heterogeneity through meta-regression, and used the trim and fill method to analyze possible publication bias in the obtained results, the credibility of the relevant results is more convincing. Our meta-analysis

results indicated that despite of an extensive analysis on datasets meeting inclusion criteria with larger study numbers and participants in experimental groups, no significant difference in mortality rates between ketamine and other sedatives was observed.

Prior to this study, two similar studies were conducted to compare the different sedative medications used in RSI. Baekgaard [30] et al. found no significant advantage of ketamine compared to other drugs for induction in trauma patients following RSI. However, a limitation of this study was the inclusion of only four papers, three of which had high/serious or moderate bias, potentially limiting the generalizability of their findings. Another meta-analysis comparing ketamine and etomidate in RSI found that, while there was no apparent difference in first-pass intubation success, etomidate had a lower incidence of post-induction hypotension compared to ketamine [31]. There have been meta-analysis of the application of sedative medications in RSI, but as previous meta-analysis have excluded cohort studies, we conducted this research with the inclusion of a larger number of patients, in the hope of providing insights into clinical practice.

Moreover, efforts should be directed towards minimizing intubation-related complications [32]. Ketamine is extensively employed in the emergency department for sedation and analgesia in pediatric emergency cases [33, 34]. Additionally, it can be used independently or in combination with propofol and other drugs for sedation in agitated adult patients [35, 36]. Jaber et al. [3] conducted an RCT comparing ketamine and etomidate in tracheal intubation of critically ill patients and the results indicated that etomidate has fewer hemodynamic effects. However, it may be associated with adrenal function suppression. The results indicated that a single administration of either ketamine or etomidate before intubation had no significant effect on the 28-day mortality, intubation conditions or SOFA scores. However, it is noteworthy that the incidence of adrenal insufficiency was lower in the ketamine group. Another study comparing early and late survival rates between etomidate and ketamine for infection patients undergoing RSI found no differences. However, etomidate was associated with a higher risk of early post-intubation vasopressor administration [21]. The results of our analysis showed that ketamine did not affect mortality within 28 days of intubation, and it was not associated with first-time intubation success, post-intubation SOFA scores, mechanical ventilation, hemodynamic changes, or complications related to tracheal intubation when compared with other sedative drugs. Sedation with ketamine during RSI, however, may reduce mortality within 7 days in critically ill patients, but may increase the length of stay in the ICU within 28 days.

Apart from ketamine, other sedatives, such as etomidate, propofol, sodium thiopental, midazolam, etc., are also employed in RSI. Etomidate, a non-barbiturate hypnotic, minimally suppresses hemodynamics and ensures optimal intubation conditions. Of note, etomidate may inhibit adrenal mitochondrial 11-β-hydroxylase activity, potentially leading to reversible adrenal insufficiency [37]. Clinical studies by Jaber and colleagues [3] have found that the use of etomidate may increase the incidence of adrenal insufficiency compared to ketamine. Previous study revealed that combining morphine with benzodiazepines was associated with a lower short-term mortality rate (within 5 days) compared to morphine combined with etomidate [4]. Additionally, compared to midazolam, etomidate might increase the use of blood products, length of stay in ICU, and ventilation time [38]. However, other research found that the use of etomidate and ketamine did not significantly impact patient mortality, ICU length of stay, or mechanical ventilation time [3].

Neuromuscular relaxants, such as rocuronium and succinylcholine, are also commonly used after sedative medications during RSI. Most of the individual studies included in this meta-analysis used both drugs as neuromuscular relaxants. Available meta-analysis have mostly focused on differences in intubation conditions after administration and have not directly explored the correlation between the different neuromuscular relaxants and disease progression or mortality [39].

Strengths and limitations

Several limitations must be acknowledged in this study. Firstly, there was considerable heterogeneity in the included studies, which enrolled critically ill patientswith trauma victims and severe infections. Additionally, patients undergoing RSI both pre-hospital and post-admission settings were included. While the broad inclusion of these patient populations may contribute to increased heterogeneity, it potentially supports the exploration of sedative choices during RSI for critically ill patients under various medical conditions. Despite our findings indicating a reduction in that mortality within 7 days after RSI with ketamine, it is important to note that the inclusion of a limited number of studies ($n=3$) necessitates further research to ascertain the generalizability of these results to clinical practice. Furthermore, our study only included sedative drugs directly compared with ketamine. The potential suitability of other sedative drugs as reference remains unexplored, warranting further investigation for optimal options in RSI. Finally, the mortality of critically ill patients after RSI is influenced by multiple factors, including not only the use of sedative drugs but also the severity of the patient's underlying condition and the overall organ function. However, the data

provided in the original articles are insufficient for a comprehensive assessment. Therefore, large-scale RCT studies are needed to provide guidance on the optimal selection of sedative drugs during RSI.

Conclusions

A meta-analysis of existing studies reveals that in the sedative drug selection for RSI in critically ill patients, ketamine does not exhibit a significant impact on in-hospital mortality compared to other sedatives. Ketamine may associate with lower in-hospital mortality within 7 days after RSI, however, it may also associate with fewer ICU-free days within 28 days. Despite the inclusion of all relevant studies regarding the use of ketamine in RSI, larger-scale randomized trials are still necessary to establish more reliable evidence.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12873-024-01094-8.

Supplementary Material 1.
Supplementary Material 2.
Supplementary Material 3.
Supplementary Material 4.
Supplementary Material 5.
Supplementary Material 6.
Supplementary Material 7.
Supplementary Material 8.

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Authors' contributions
Author contributions: Qinxue Hu analyzed the data and drafted the first version of the manuscript; Xing Liu conceptualized the study; Xing Liu and Chengli Wen conducted the database search strategy; Tao Xu supervision of data collection; Li Liu and Jianguo Feng reviewed and edited the manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article and its supplementary information files.

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Competing interests
The authors declare no competing interests.

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